REMARKS

This is responsive to an Office Action mailed on June 16, 2005. In the Office Action, the Examiner rejected claims 1, 2, 4-11, 14, 15 and 21-28. Claims 1, 2, 4-11, 14, 15 and 21-28 are pending in the application. Applicants respectfully request entry of this Response After Final as the arguments presented place the application in better condition for appeal. Reconsideration of the claims is respectfully requested.

Claims 1, 2, 9, 14, and 21 were rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1, 8, 10, 13, 15, 34, 35, and 38-40 of co-pending Application No. 09/186,810. Applicants will consider filing a terminal disclaimer if both the present application and copending Application No. 09/186,810 issue into patents.

Claims 25 and 28 are rejected under 35 U.S.C. §102 (b) as being anticipated by Cahalan (US 5,308,641). The Examiner alleged that the U.S. Patent No. 5,308,641 (hereinafter the "Cahalan patent") anticipates claim 25 under 35 U.S.C. § 102(b). In the Office Action, the Examiner alleged that the Cahalan patent discloses human or animal tissue used as a solid surface and the biomolecule is one of the growth factors listed on column 6, lines 14-18, the abstract, column 4, lines 20-43 and column 6, lines 8-28. The Examiner also alleged that glutaraldehyde is disclosed as a crosslinking agent at column 4, lines 58-62 and that when glutaraldehyde contacts the tissue solid surface, the glutaraldehyde inherently crosslinks resulting in the crosslinked or fixed tissue as claimed.

Applicants respectfully disagree with the Examiner that claim 25 is anticipated by the Cahalan patent. An element of claim 25 is associating an exogenous polypeptide growth factor with crosslinked natural tissue. The Cahalan patent does not disclose associating an exogenous polypeptide growth factor with crosslinked natural tissue.

The Cahalan patent discloses a lightly crosslinked spacer (polyalkylimine that is attached to a solid surface) for the purpose of improving biocompatibility. (Col. 4, lines 14-19). The polyalkylimine is first applied to the solid surface and then is treated with

the crosslinking agent. (Col. 6, lines 29-31). The polyalkylimine is reacted with a crosslinking agent such that the reaction is completed in a few minutes. (Col. 5, lines 9-10) The crosslinking agent is used to lightly crosslink the polyalkylimine for the purpose of providing a polyalkylimine surface that allows a cellular adhesive molecule or other biomolecules to bond to the spacer. (Col. 4, line 62 – Col. 5, line 3; Col. 6, lines 8-10).

There is no disclosure in the Cahalan patent of a crosslinked natural tissue for association with an exogenous polypeptide growth factor. While the Cahalan patent does disclose a crosslinking agent, as the examiner alleges in the office action, the Examiner fails to take into account the portion of the Cahalan patent, following the passage upon which the Examiner relied, that discloses the crosslinking is to be limited to the spacer molecules. The Cahalan patent discloses as follows:

> The spacer of the present invention can therefore be made by applying a polyalkylimine to the solid surface and then **treating the applied polyalkylimine with the cross-linking agent**. Preferably, the cross linking agent used to **crosslink the polyalkylimine** is applied in a dilute solution and at a suitable pH to **accomplish light crosslinking** and to provide functionality for the polyalkylimine surface that will allow biomolecules to readily bond to the spacer.

(Col. 4, line 62-Col. 5, line 3)(Emphasis added). There is no disclosure in the Cahalan patent of a crosslinked natural tissue as alleged by the Examiner. Rather, the Cahalan patent discloses a lightly crosslinked polyalkylimine spacer. Polyalkylimine, the only material that is disclosed as being crosslinked in the Cahalan patent, is not a natural tissue. Therefore, the Cahalan patent does not anticipate claim 25.

Contrary to the Examiner's allegation in the Response to Argument section of the Office Action, polyalkylimine is not a natural tissue because it bonds to natural tissue. To make this assertion would lead the examiner to conclude that a titanium plate inserted into a bone would be natural tissue once the bone and the titanium plate bonded. Just as one would not consider titanium to be a natural tissue, polyalkylimine cannot be considered a natural tissue just because it attaches to natural tissue.

The Examiner alleges that the low molar glutaraldehyde solution as disclosed in the Cahalan patent **inherently** crosslinks with the natural tissue. To allege inherency, the Examiner must meet the burden of proof that what is asserted must necessarily happen. *See* M.P.E.P. § 2112.

"The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier,* 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed Cir. 1999). "In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

The Examiner alleges that when it (glutaraldehyde) contacts the tissue solid surface, it (glutaraldehyde) inherently crosslinks, resulting in a crosslinked or fixed tissue as claimed. However, the Examiner has not provided any technical reasoning to reasonably support the assertion that a low concentration glutaraldehyde solution will crosslink with tissue in the few minutes, as set forth in Cahalan. (Col. 5, lines 3-10). *See Ex parte Levy,* 17 USPQ2d at 1464.

The Examiner also relied upon Example 1 in U.S. Patent No. 4,648,881 to Carpentier et al. Example 1 in the Carpentier patent disclosed that porcine aortic heart valve tissue was fixed with 0.625 weight percent solution of glutaraldehyde. However,

there is no indication of the amount of time that was necessary to fix the porcine aortic heart valve with the glutaraldehyde solution.

Applicants do not dispute that with enough time and at adequate concentrations, glutaraldehyde will fix a tissue as disclosed in the Carpentier patent. However, Applicants do dispute that a low concentration glutaraldehyde solution will crosslink with tissue in the few minutes disclosed in the Cahalan patent.

Applicants have previously provided the Examiner with an excerpt from Collagen Volume III, Biotechnology, CRC Press, pp. 2, 3 and 13 which indicates that fixing tissue with glutaraldehyde takes hours to occur. An additional copy of the excerpt is attached hereto as Exhibit A for the Examiner's review. Thus, Applicants have provided third party technical data that indicates that crosslinking or fixing a natural tissue with glutaraldehyde requires several hours to complete, not just a few minutes as in Cahalan. The Examiner's posits or any other allegation, without a basis in fact and/or technical reasoning, does not support an allegation of inherency. *See Ex parte Levy,* 17 USPQ2d at 1464. Therefore, the Examiner has not satisfied the burden of proof to allege that a low molar glutaraldehyde solution fixes a natural tissue in a few minutes as in Cahalan

For at least these reasons, the Cahalan patent does not anticipate claim 25. Reconsideration and allowance of claim 25 are respectfully requested.

Since claim 25 is not anticipated by the Cahalan patent, the anticipation rejection of claim 28, which includes all of the elements of claim 25, is moot. Therefore, Applicants respectfully request that the Examiner withdraw the anticipation rejection of claim 28 over the Cahalan patent.

Claims 25 and 26 are rejected under 35 U.S.C. §102 (b) as being anticipated by European Patent Application No. 0476983 (hereinafter the "Bayne application") or alternatively, under 35 USC 103(a) as being unpatentable over the Bayne application alone. The Examiner alleged the Bayne application discloses a fibrin coating being applied prior to or in addition to a VEGF II growth factor to a surface of a fixed umbilical

cord vein. The Examiner also speculates (posits) that the tubular supports coated with VEGF II include fixed umbilical cord vein and this anticipates claim 25 where the attachment of the cells to the vessel is done prior to implantation such that the claim language requiring growth factor associated with the tissue is fully met.

Applicants respectfully disagree with the Examiner's characterization of the disclosure of the Bayne application. The Bayne application does not disclose a fibrin coating being applied prior to or in addition to a VEGF II growth factor to a surface of a fixed umbilical cord vein. Rather, the Bayne Application discloses growing cells in a culture in the presence of VEGF II, removing the cells from the culture and plating the cells on fixed umbilical cord vein.

The Bayne application does not disclose associating an exogenous polypeptide growth factor with crosslinked natural tissue, elements of claim 25. Therefore, the Bayne Application does not disclose each and every element of claim 25. As such the Bayne Application does not anticipate claim 25.

The Examiner also alleged that the Bayne application makes claim 25 unpatentable as being obvious. The Examiner posits (assumes) that it would have been clearly obvious to use umbilical cord vein as the tubular support since it is used as an implant in another procedure; it would bring the desired features of tissue properties to the implant site. Furthermore, a combination of proteins such as a fibrin, and growth factor (VEGF II) would have been at least obvious in view of the Bayne application alone since the teachings of doing the same are all contained in the same paragraph and there is no clear delineation between them.

Applicants respectfully disagree with the Examiner that claim 25 is obvious over the Bayne Application. The Examiner has failed to meet his initial burden of establishing a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P §2142. The Examiner's assumption used to allege that claim 25 is obvious does not meet the standard for modifying a reference as set forth in case law.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Applicants submit that the Examiner used the language of claim 25 as a roadmap to combine aspects of two separate preparation procedures disclosed in the Bayne application for implanting two dissimilar materials, a natural vessel and an artificial vessel. Of note, claim 25 is directed to a prosthetic comprising crosslinked **natural** tissue. Therefore, the procedure for preparing an **artificial** vessel is not relevant to claim 25.

The Examiner combined associating fibrin and growth factor, which was disclosed as being coated on an **artificial** vessel, with the preparation of a **natural** tissue (fixed umbilical cord vein). However, the Bayne application only discloses coating the **natural** tissue (fixed umbilical cord vein) with endothelial cells prior to implanting. There is no teaching or suggestion to combine a method of preparing an **artificial** vessel with a method of preparing a **natural** tissue, absent the present invention, which is impermissible.

The Examiner's reasoning for combining the two separate and dissimilar procedures for preparing dissimilar materials is "the teaching of doing the same are all contained in the same paragraph and there is no clear delineation between them." (Office Action mailed on June 16, 2005, p. 4). A statement that modifies the prior art to

meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). The mere fact that elements of a claim are located in the same reference in proximity to each other does not meet the Examiner's burden for modifying the reference.

Further, Applicants disagree with the Examiner's characterization of the Bayne application that the two separate and distinct procedures are not delineated. The Bayne application at page 8, line 20 starts the sentence with the word "Alternatively." By definition, the word "alternative" means a choice between two mutually exclusive possibilities. *See* The American Heritage Dictionary of the English Language, p.55, Houghton Mifflin Company, (3rd Ed. 1992) attached hereto as Exhibit B. Where two choices are mutually exclusive or alternatives, the two procedures cannot be combined.

Finally, the Examiner posits (assumes) that since umbilical cord vein is used as an implant in another procedure, it would bring the desired features of tissue properties to the implant site. The Bayne Application discloses how to prepare both a natural vessel (coating with endothelial cells only) and an artificial vessel (coating with proteins such as fibrin and a growth factor (VEGF II)) by distinctly different and mutually exclusive procedures. There is no teaching in the Bayne application to combine the two distinctly separate procedures for preparing dissimilar materials for implantation. Therefore, the Bayne application alone does not make claim 25 obvious.

Since claim 25 is neither anticipated or made obvious by the Bayne Application, claim 26, which depends from claim 25, is also not anticipated or made obvious by the Bayne Application. Therefore, Applicants respectfully request that the Examiner withdraw the anticipation and obviousness rejections of claims 25 and 26 over the Bayne application.

Claims 1-2, 4-5, and 9-11 are rejected under 35 U.S.C. §103 (a) as being unpatentable over the Bayne application in view of U.S. Patent No. 5,631,011 (hereinafter the "Wadstrom patent"). The Examiner alleged that the Bayne application discloses an implant having a fibrin coating (a biologic adhesive as claimed) which is applied prior to the VEGF II growth factor. The Examiner also alleged that fixed umbilical cord vein as disclosed in the Bayne application is the substrate for coating as claimed. The Examiner alleged that the fixed umbilical cord as disclosed in the Bayne application, while not clearly an allograft or a xenograft, is generic to both. The Examiner finally alleges that it would have been considered clearly obvious to an ordinary artisan to use an allograft or xenograft tissue for the cord vein as disclosed in the Bayne application absent some showing of criticality therefore. The Examiner alleges that the Wadstrom patent discloses that fibrin is a common biologic tissue adhesive in the art and therefore, the fibrin coating as disclosed in the Bayne application would function as a biologic adhesive as claimed.

Applicants respectfully disagree with the Examiner that claim 1 is obvious over the Bayne application in view of the Wadstrom patent. Elements of claim 1 include a prosthesis for a human patient comprising **allograft or xenograft** tissue having polypeptide growth factor associated therewith. An allograft tissue is defined in the specification as tissue of a different individual of the same species. (Page 8, lines 21-23). A xenograft tissue is defined in the specification as tissue from a species different from the patient's species. (Page 8, lines 19-21). Therefore, allograft tissue and xenograft tissue are natural tissues.

The Examiner again improperly combined the two mutually exclusive preparation procedures, one for natural tissue and one for an artificial vessel, disclosed in the Bayne application to improperly allege that the Bayne application discloses coating fixed umbilical cord vein with fibrin and growth factor. Applicants incorporate the arguments made above with respect to claim 25 and the Bayne application to show that the Examiner improperly modified the Bayne application and that the Examiner has not

met his burden of proving prima facie obviousness.

To reiterate, the Bayne application does not disclose coating fibrin and growth factor on fixed umbilical cord vein. Rather, the Bayne application discloses coating fibrin and growth factor on an artificial vessel. An artificial vessel is neither an allograft tissue nor a xenograft tissue as defined in claim 1. Therefore, the Bayne application does not disclose allograft tissue or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive such as fibrin.

The Wadstrom patent does not disclose allograft tissue or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive such as fibrin. While the Examiner alleges that the Wadstrom patent is being utilized similar to that of a dictionary definition for fibrin, the Examiner has not explained how the use of fibrin can be incorporated into the procedure for a natural tissue as disclosed in the Bayne application. The Bayne application does disclose coating an artificial vessel with fibrin. However, an artificial vessel is not an allograft or xenograft tissue as defined in claim 1. Therefore, the combination of the Bayne application with the Wadstrom patent is not proper to allege that claim 1 is obvious. Reconsideration and allowance of claim 1 are respectfully requested.

Claims 2, 4-5 and 9-11 were also rejected as being obvious over the Bayne application in view of the Wadstrom patent. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1 above.

Claims 6-8, 14,15, 21-24, and 27-28 are rejected under 35 U.S.C. §103 (a) as being unpatentable over the Bayne application and the Wadstrom patent as applied to claims 1-5, 9-11, and 29 (25?) above, and further in view of the Carpentier patent. The Examiner alleged that the while the Bayne application fails to disclose uncrosslinked tissue, the heart valve form of tissue, or other types of tissue claimed, the Carpentier patent teaches that all uncrosslinked and crosslinked forms of tissue, heart valve tissue forms and other types of tissue are known in the art. The Examiner then alleges that it

would have been obvious to use any of the materials disclosed in the Carpentier patent as the substrate of the Bayne application for the applications contemplated by the Carpentier patent. The Examiner also alleged that one would be motivated to form the implants disclosed in the Bayne application into other shapes to make it useful in other sites and broaden its applicability.

Applicants respectfully disagree with the Examiner that claim 14 is obvious over the Bayne application in view of the Wadstrom patent and the Carpentier patent. Again, the Examiner improperly modified the Bayne application to combine mutually exclusive methods of preparing a **natural** tissue for implantation with the method for preparing an **artificial** vessel for implantation as previously discussed with respect to independent claims 1 and 25.

The Carpentier patent discloses many different **natural** tissues that can be used as heart valve prostheses. (Emphasis added). There is no reason to combine the tissues disclosed in the Carpentier patent with the mutually exclusive method of preparation disclosed the Bayne Application for an artificial substrate. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

The tissue disclosed in the Carpentier patent is natural tissue. As such, the tissue disclosed in the Carpentier patent as applied to the disclosure of the Bayne application would be prepared by plating cells that were grown in vitro in a VEGF II solution, and then the tissue would consequently be implanted into the patient.

The combination of the Bayne application with the Carpentier patent would not provide a natural tissue heart valve comprising a substrate associated with VEGF. Therefore, the Bayne application in view of the Wadstrom patent and the Carpentier patent does not make claim 14 obvious.

Further, the Examiner improperly used claim 14 as a roadmap to allege obviousness. Claim 14 relates to a prosthetic heart valve. The Examiner cites the Bayne application as the primary reference. However, the Bayne application does not disclose the implanting of a heart valve, but rather the preparation of artificial and natural blood vessels for implantation.

In fact, when this issue was addressed in the previous amendment, the Examiner responded that the motivation to combine the references was"[o]ne would be motivated to form Bayne et al implants into other shapes in order to make it useful in other sites and broaden its applicability." (See Office Action mailed on June 16, 2005, 2004, p. 5). The Examiner's stated purpose for combining the Bayne application with the Carpentier patent is an improper combination.

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Broadening the applicability of a reference beyond its disclosure is not a permissible reason to combine references. As such, the combination of the Bayne application and the Wadstrom patent with the Carpentier patent is an improper combination.

For the foregoing reasons, claim 14 is not made obvious over the Bayne application in view of the Wadstrom patent and the Carpentier patent. As such, reconsideration and allowance of claim 14 are respectfully requested.

Claims 15 and 21-24 depend from independent claim 14. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1, 14, and 25 above.

Claims 6-8 depend from independent claim 1. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that

these rejections are moot in view of the remarks made in connection with independent claim 1 above.

Claims 27-28 depend from independent claim 25. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 25 above.

Conclusion

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at 612-334-3222.

The Director is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

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